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Case Report

INTERSTITIAL DELETION OF THE LONG ARM OF CHROMOSOME 11: REPORT OF A CASE AND REVIEW OF THE LITERATURE

Akihiro WAKAZONO,[1,2] Mitsuo MASUNO,[1] Seiji YAMAGUCHI,[1] Kouji TSUBOUCHI,[2] Naomi KONDO,[1] and Tadao ORII[1]

[1]*Department of Pediatrics, Gifu University School of Medicine, Tsukasa-machi, Gifu 500, Japan*
[2]*Division of Pediatrics, Hashima Municipal Hospital, 3–246 Shinsei-cho, Hashima 501–62, Japan*

Summary A 12-month-old female infant with developmental delay, growth retardation, and dysmorphic features including dolichocephaly, telecanthus, ptosis, flat nasal bridge, anteverted nares, high-arched palate, carp-shaped mouth, micro-retrognathia, and low-set and posteriorly rotated ears was found to have an interstitial deletion of chromosome 11 involving bands q14-q22. Immunoblot analysis of her fibroblasts revealed a normal amount of mitochondrial acetoacetyl-coenzyme A thiolase, of which gene locus has been assigned to chromosome 11q22.3-q23.1. This result suggested that the region around the boundary of 11q22.3-q23.1 was intact in this patient.

Key Words interstitial deletion, 11q, 11q−, del(11)(q14q22)

INTRODUCTION

To date, at least 8 patients with an interstitial deletion of chromosome 11q (11q13-q23) have been documented (Taillemite *et al.*, 1975; Sørensen *et al.*, 1979; McPherson and Meissner, 1982; Taki *et al.*, 1983; Bateman *et al.*, 1984; Klep-de Pater *et al.*, 1985; Carnevale *et al.*, 1987; Okamura *et al.*, 1988). Here we report a patient with an interstitial deletion of 11q14 to q22.

CASE REPORT

The proposita, one of a pair of twins of different sex, was born to a 28-year-old gravida 3, para 2 mother and an unrelated 32-year-old father. Both parents, two

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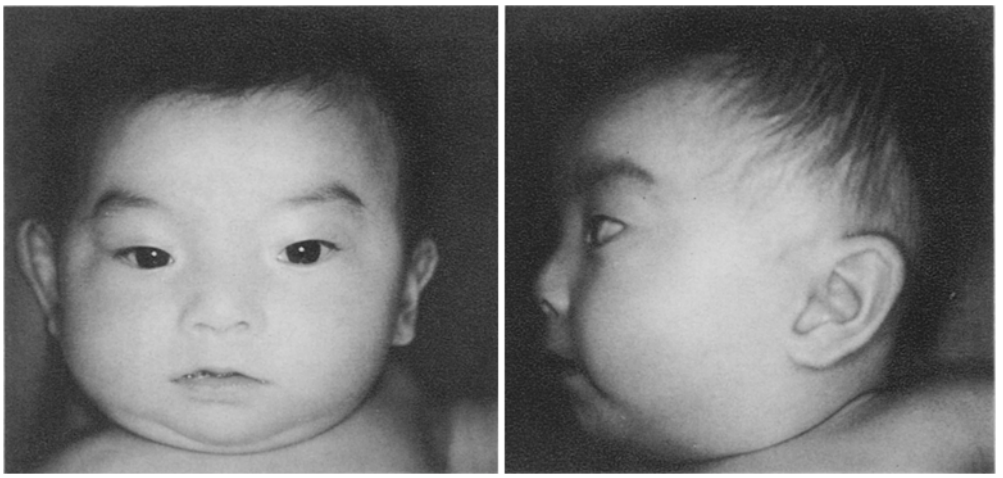

Fig. 1. Front and lateral views of the proband, aged 5 months.

elder brothers and the other twin were all normal and healthy. Because of fetal distress, a cesarean section was performed at 36 weeks of gestation. The Apgar score was 9 at 1 min. Birth weight was 2,596 g, length 45.0 cm, and the head circumference 33.5 cm. She had an apnea attack at 10 hr after birth. With resuscitation treatment and intravenous administration of theophylline, her clinical findings improved. Her early neonatal period was complicated by transient hypocalcemia, generalized hypotonia, an occasional apneic attacks, and feeding difficulties. Her craniofacial features included dolichocephaly, telecanthus, bilateral blepharoptosis, flat nasal bridge, anteverted nares, high-arched palate, carp-shaped mouth, micro-retrognathia, and low-set and posteriorly rotated ears (Fig. 1). She had no abnormality in anterior segment, media, and ocular fundus. Computerized tomography of the head and echocardiogram findings revealed no abnormalities.

She controlled her head at 5 months of age, rolled over at 9 months, and sat alone at 10 months. She was repeatedly hospitalized for respiratory infections. Immunological tests were normal including serum IgG, IgA, IgM, and IgE concentrations, lymphocyte responses to phytohemagglutinin and concanavalin A, and relative counts of T-subset lymphocytes (CD3, CD4, CD8, and CD19). At the age of 12 months, she weighted 7,335 g (-2.2 S.D.), height 63.5 cm (-4.7 S.D.), and head circumference 44.0 cm (-0.6 S.D.). She was barely able to stand with support. Her developmental quotient was 59.

CYTOGENETIC FINDINGS

GTG high resolution chromosome analysis (Ikeuchi, 1984) on peripheral lymphocyte cultures from the proposita revealed an interstitial deletion involving

about two-thirds of bands 11q14-q22. The boundaries of the bands 11q13-q14, and of 11q22-q23 seemed to be intact (Fig. 2). Chromosomes of cultured skin fibroblasts confirmed the finding. Her parents and twin brother all had normal chromosomes.

IMMUNOBLOT ANALYSIS

We recently assigned the locus of the gene for human mitochondrial acetoacetyl-coenzyme A thiolase (T2) to 11q22.3-q23.1 by fluorescence *in situ* hybridization (Masuno *et al.*, in press). In a family that contained a patient with deficient T2 (3-ketothiolase deficiency; McKusick 203750), a heterozygote was distinguishable from a normal subject using immunoblotting (Fukao *et al.*, 1991). The immunoblot analysis was performed by the use of both anti-[rat mitochondrial acetoacetyl-coenzyme A thiolase (T2)] IgG and anti-[rat mitochondrial 3-ketoacyl-coenzyme A thiolase (T1)] IgG. In cultured skin fibroblasts of the proposita, the intensity of the signals for both T2 and T1 was essentially the same as that in a control subject (Fig. 3). The activity of T2 in her fibroblasts was within the normal

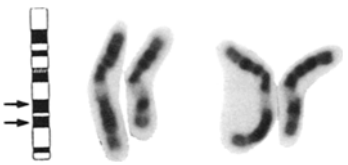

Fig. 2. Two G-banded partial karyotypes of the proposita. The deleted chromosome 11 is on the right. An idiogram of chromosome 11 is shown with the breakpoints of the deletion shown in bands q14 and q22.

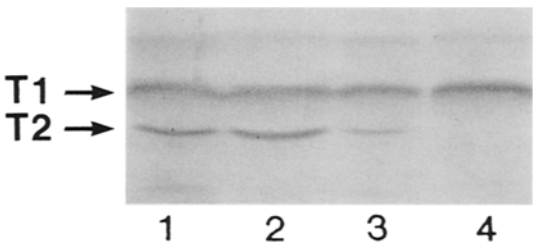

Fig. 3. Immunoblots of mitochondrial 3-ketoacyl-CoA thiolase (T1) and acetoacetyl-CoA thiolase (T2) in fibroblasts. Lane 1, fibroblasts from a normal control; lane 2, the present patient; lane 3, a heterozygote of 3-ketothiolase deficiency (the father of a 3-ketothiolase deficiency patient); and lane 4, a patient with 3-ketothiolase deficiency. Arrows indicate the subunits of T1 and T2, respectively. A mixture of anti-rat T1 and anti-rat T2 was used as the first antibody in this immunoblot analysis.

Table 1. Thiolase activities in fibroblasts from the patient.

Substrate	Acetoacetyl-CoA			3-Ketooctanoyl-CoA
	+K	−K	+K/−K	
Patient	6.8	3.6	1.9	7.9
Control	9.1	4.4	2.0	9.8
(range n=15)	(6.6–11.9)	(3.2–6.3)	(1.8–2.4)	(6.9–12.9)

Thiolase activity is expressed as nmol of substrate breakdown/min/mg protein. Abbreviations: +K and −K, acetoacetyl-CoA thiolase activity in the presence and absence of potassium ion, respectively; +K/−K, ratio of +K/−K.

range (Yamaguchi *et al.*, 1988) (Table 1). The region around the boundary of 11q22.3-q23.1 in the patient is thus likely to be intact.

DISCUSSION

The first observation of a terminal deletion of the long arm of chromosome 11 was that of Jacobsen *et al.* (1973). Since then, about 30 other cases have been reported. All of the patients had severe mental retardation with characteristic craniofacial features. The critical region compatible with the typical 11q terminal deletion syndrome is thought to be a subband of 11q24.1 (Fryns *et al.*, 1986). On the other hand, there have been some cases of an interstitial deletion of 11q (q13-q23), and they showed less pronounced or absent signs of the 11q terminal deletion syndrome (Taillemite *et al.*, 1975; Sørensen *et al.*, 1979; McPherson and Meissner, 1982; Taki *et al.*, 1983; Bateman *et al.*, 1984; Klep-de Pater *et al.*, 1985; Carnevale *et al.*, 1987; Okamura *et al.*, 1988). Table 2 shows a review of the clinical features of the patients with interstitial deletion of 11q, including ours, and a comparison of those with the 11q terminal deletion syndrome. Six cases showed mental retardation, another three cases showed normal psychomotor development. The patient reported by Bateman *et al.* (1984) showed only Peters' anomaly. Clinical features such as mild or absent growth and psychomotor retardation, hypertelorism, ptosis, ocular anomalies, flat nasal bridge, cleft palate, cleft lip, micro-retrognathia, high-arched palate, low-set and malformed ears, abnormal fingers and toes, hypotonia, and cardiac anomalies have commonly been described. However, those are not sufficient features for a clinically recognizable syndrome. To evaluate the exact karyotype-phenotype correlation, it is necessary to perform molecular analysis in those patients with varied segments of interstitial deletion of 11q.

The gene for ataxia-telangiectasia, characterized by immunodeficiency, was localized to chromosome 11q22-q23 (McConville *et al.*, 1990). Although our case suffered from recurrent respiratory infection, she had, upon examination, normal immunological functions.

A tumor suppressor gene has also been assigned to within the 11q13-q23 region

Table 2. Clinical comparison of the present patient with monosomy 11q(q13-q23).[a]

	1	2	3	4	5	6	7	8	Present case	Total	Terminal deletion[b]
Sex	F	M	M	F	M	F	F	F	F	6F/3M	22F/7M
Age	23M	15M	5W	5Y	18M	5Y	7.9Y	10M	12M		
Gestation	term	term	term		38W	36W			36W		
Birth weight	3,420 g	3,500 g		3,460 g	2,700 g	2,890 g	2,350 g	2,600 g	2,596 g	Mean: 2,939 g	2,692 g
Growth retardation	+		−	+	+	−	−	−	+	4/8	
Mental retardation	+	+	−	+	+	−	+	−	+	6/9	22/22
Craniofacial region											
Trigonocephaly		+	−	−		+			−	2/5	20/25
Dolichocephaly			−					+	+	2/3	3/8[c]
Hypertelorism	+		−		+	+	+		−	4/6	19/24
Telecanthus			−					+	+	2/3	4/5[c]
Epicanthus		+	−	+					−	2/4	15/23
Ptosis			−	+	+		+		+	4/5	11/15
Strabismus		+	−	+		+			−	3/5	4/5
Antimongoloid slant	+								−	1/2	10/23
Ocular abnormalities			+	+	+	+			−	4/5	
Flat nasal bridge	+	+	−	+		+	−	+	+	6/8	14/15
Short bulbous nose			−				+		−	1/3	21/21
Cleft palate/lip	−	−	−	+/−	+/−	+/+	+/−	+/+	−	5/9	
Micro/retrognathia	+		−	+	+			+	+	5/6	20/23
Carp-shaped mouth			−	+	+	−			+	3/5	18/19
High-arched palate		+	−		+		+		+	4/5	10/10[c]
Low-set/malformed ears	+	+	−	+		+	−	−	+	5/8	24/26
Abnormal fingers/toes			−	−	+	+	+	+	−	4/7	23/24
Hypotonia				−	+		+	−	+	3/5	
Cardiac abnormalities	+	−	−	−	+	+	−	+	−	4/9	16/23
Breakpoints	q14.1 q22.1	q14q22	q14q22	q14.2 q23.2	q21q23	q13q21 or q21q23	q13q21 or q21q23	q13q21 or q21q23	q14q22		
De novo deletion	+	+	+		+	+		+	+		

[a] 1, Taillemite *et al.*, 1975; 2, Sørensen *et al.*, 1979; 3, Bateman *et al.*, 1984; 4, Okamura *et al.*, 1988; 5, Taki *et al.*, 1983; 6, McPherson and Meissner, 1982; 7, Klep-de Pater *et al.*, 1985; 8, Carnevale *et al.*, 1987. [b] Frequencies are found in the patients with 11q terminal deletion syndrome cited from the data by Klep-de Pater *et al.* [c] Cited from the data by Helmuth *et al.*

(Misra and Srivatsan, 1989). This patient may lack this suppressor gene, and hence it is important to observe her condition concerning tumorigenecity with time. Construction of a somatic cell hybrid from our patient with del(11)(q14q22) will contribute to isolating this tumor suppressor gene.

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